Citation:

Hilary Green J, Richards JK, Bunning RL. Blood pressure responses to high-calcium skim milk and potassium-enriched high-calcium skim milk. J Hypertens. 2000 Sep;18(9):1331-9.

PubMed ID: 10994765

Study Design:

Randomized double blind controlled trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

This study was designed to evaluate the effect of high-calcium skim milk or potassium enriched high calcium skim milk on blood pressure compared with non enriched skim milk.

Inclusion Criteria:

- Healthy people, aged 40 or older
- Willingness to replace usual liquid milk with 2 servings per day of skim milk(control), high calcium skim milk or potassium enriched high-calcium skim milk.
- All volunteer gave their informed, written consent to the procedureswhich were approved by the Massey University Human Ethics Committee.

Exclusion Criteria:

- Less than 40 years of age
- Took calcium or potassium supplements
- Taking medication for high blood pressure
- Anyone with a sitting blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic to consult his or her general practitioner. They subsequently remained in the trial only if they received no pharmaceutical treatment for raised blood pressure.

Description of Study Protocol:

Recruitment : details were not provided

Design : Randomized, double-blind,controlled cross over study

Blinding used: double blind study

Intervention

- Usual milk intake was replaced for 4 weeks with 2 servings/day ad libitum with one of three milks with different compositions: two were commercially available and these were Skim Milk Powder(SMP)(control) and high calcium SMP.
  - The third milk powder was the same high-calcium intow which potassium bicarbonate had been dry-blended.
  - The milk was provided to the volunteers as a dry powder.
  - On a daily basis, 50g of powder was reconstituted with tap water to provide two servings (480 ml) of liquid milk

Table 1 Mineral composition of the milk powders

	SMP	High-calcium SMP	Potassium-enriched high-calcium SMP
Calcium(mg/50g)	720	1075	1040
Potassium (mg/50 g)	885	855	1585
Magnesium (mg/50 g)	64	74	71
Sodium (mg/50 g)	197	208	195

SMP, skim milk powder

· The amount of calcium provided by drinking water in Pamerston North ranges from 6-36 mg/l. depending on location within the city. Therefore the tap water used to reconstitute the milk powder would have provided 3-17 mg calcium/day.

- Each 4 week period was separated with a 4 week washout period.
- Each volunteer consumed the milks in random order.

Statistical Analysis

- The impact of milk on blood pressure was evaluated using a cross-over repeated measures analysis of variance(general linear models procedure) and post hoc comparisons of means carried were carried out by lest squares means
- Differences between baseline and end of trial characteristics were assessed sing a paired Student's t test.
- Correlations were performed by Pearson product moment.
- Results are expressed as mean ±SD.

Data Collection Summary:

Timing of Measurements

- Baseline
  - office BP
  - 24 hour urine
  - Exercise test

- Anthropometrics
- Start and end of each 4 week intervention: ambulatory BP
- First week of first intervention:
  - 24 hour recall
  - 24 hour urine collection following recall
- After 2 weeks of each intervention:
  - office BP
- End of each 4 weeks intervention:
  - office BP
  - 24 hour urine
- First week of third intervention
  - 24 hour recall
  - 24 hour urine collection following recall
- End of study
  - Exercise test
  - Anthropometrics

Dependent Variables

- Blood pressure
  - Office blood pressure measurements were made with the subjects both seated and standing, each after a 10 min rest period in each position. In order to minimize observer bias, researchers used an automated oscillometric blood pressure monitor (A&D, Model UA-751; A&D Medical Division, Milpitas, California, USA). The manufacturers claim that this monitor was accurate to ± 3 mmHg or 2% which ever is greater.
  - Ambulatory blood pressure was measured at start and end of each intervention using an ambulatory blood pressure monitor (Dynapulse DP5000A, PULSE Metric Inc, San Diego, California, USA). The manufactures claimed that this monitor was accurate to 5 mmHg, thereby meeting ANSI/AAMI standards

- Urinary mineral excretion
  - The urine collections were analyzed for urea, creatinine, ammonia and uric acid to determine nitrogen excretion using standardized methodologies.
  - Potassium and sodium were measured by flame photometry and all other minerals were measured by spectrophotometry using commercially available kits.
  - Urea, creatinine, ammonia, uric acid, calcium and magnesium were measured using standardized methodologies.

Independent Variables

- test milks: high-calcium skim milk, potassium-enriched high-calcium skim milk, or skim milk powder

Control Variables

Physical characteristics

- Age(years)
- Body Weight (kg)- measured using a beam balance to the nearest 0.2 kg
- Height- standing height was measured using a stadiometer to the nearest 0.1 cm.

- Body mass index (kg/m^2)
- Body fat(% body weight)
- Waist and Hip circumference-measured to the nearest 0.1 cm using a measuring tape.
- Lean body mass was measured by total body bioelectrical impedance(Biodynamics Model 310, Seattle Washington, USA) after at least 3 hours without food or drink.

Physical exercise:

- Subjects were asked pedal at 60rpm for 3 minutes at three consecutive, submaximal workloads using a cycle ergometer (Monark Ergomedic 818E, Monark Bodyguard, Sweden).
- Heart rate was measured during the last 10 seconds of each workload using a telemetric data logging device(Mini-logger series 2000;Mini MITER, Sunriver, Oregon, USA).
- Oxygen consumption at each workload was calculated using a validated predictive equation and maximum oxygen consumption was estimated using linear regression of heart rate and oxygen consumption, with the assumption that maximum heart rate was 220-age in years.

Diet

- The food intakes were analyzed for macro- and micronutrient content using the New Zealand Food Composition Database, which was assessed using nutrient analysis software (FOODworks v2, Xyris Software Pty Ltd, Highgate Hill, Queensland, Australia).
- Under-reporters were identified by comparing reported dietary intakes of protein(from which the researchers derived nitrogen intake) and energy against urinary nitrogen excretion and basal metabolic rate.

-Basal metabolic rate was calculated using the Schofield's equations from measurement of height and weight and age.
-The two cut-off tests were (i) Urine UN:NI(urinary nitrogen: nitrogen intake) and (ii) EI: BMR(energy intake:basal metabolic rate. Anyone not meeting these criteria was deemed to be under-reporting their protein and/or energy intake.

Description of Actual Data Sample:

Initial N: 38 (19 females;19 males)

Attrition (final N): 38

Age: 50-66 years

Ethnicity: Caucasian, except for 1 Polynesian women.

Other relevant demographics:

Anthropometrics : There were no statistical differences between groups.

Location: Massey University, Palmerston, New Zealand

Summary of Results:

Key findings:

- Office sitting SBP did not change after either SMP or high-calcium SMP, but after 4 weeks of the potassium-enriched high-calcium milk, it decreased from 125±18 to 117±16 mmHg (P<0.001)
- In the standing position, office SBP decreased after 4 weeks of each of the milk interventions.
- After SMP, standing SBP decreased from 127±16 to 124±16 mmHg (P<0.05); after high-calcium SMP, it decreased from 130±18 to 126±17 mmHg (P<0.05); and after potassium-enriched hig-calcium SMP, it decreased from 130±16 to 122±15 mmHg (P<0.001).
- Mean 8 hour ambulatory blood pressures were unchanged after either SMP or high calcium milk. After potassium-enriched high-calcium milk, ambulatory systolic and diastolic blood pressures decreased: systolic, from 138±13 versus 135±11 mmHg (P<0.05) and diastolic, from 80±8 to 78±9 mmHg (P<0.05)

Other Findings:

- There was no difference in excretion rates of calcium or potassium after any of the milk interventions.
- Sodium excretion decreased from 11.58+4.13 to 10.75 mmol/mmol creatinine (P<0.05) after the potassium-enriched high caclium SMP (P<0.05).
- Magnesium excretion decreased from the baseline of 0.40_0.15 to 0.35+0.12 mmol/mmol creatinine after SMP (P<0.05), but the latter value was not significantly different from the other two baseline values.
- There was no difference in energy, macro- or micronutrient intake between individuals. Usual intake (mean of start and end of trial estimations) of calcium ranged from 0.33-3.18 g/day, usual intake of potassium ranged from 2.00-7.40 g/day and usual intake of sodium ranged from 1.00-4.65 g/day (Table 3).
- The mean levels of both systolic and diastolic blood pressure were within the normal range, the group included people with a wide range of blood pressures. Seated office blood pressures measured by sphygmomanometer at the end of the last washout period ranged from 99-168 mmHg, systolic and 63-102 mm Hg, diastolic.
- The baseline measurement of sitting systolic blood pressure was lower at the start of the skim milk powder (SMP) intervention than at the start of the high –calcium SMP intervention (121±14 versus 125±19 mmHg; P< 0.05). There were no significant differences in the other baseline measures.

Table: Office and Ambulatory Blood Pressure Changes:

	Skim milk		High-calcium skim mill		Potassium-enriched high-calcium skim milk	
	Start	End	Start	End	Start	End
Office, sitting						
SBP (mmHg)	121±14	122±15	125±19	122±13	125±18	117±16***

DBP (mmHg)	77±9	76+9	77±10	75±9	78±10	76±11
Office, standing						
SBP (mmHg)	127±16	124±16*	130±18	126±17*	130±16	122±15***
DBP (mmHg)	85±10	83±10	85±10	83±9	85±10	83+10
Ambulatory 8h mean						
SBP (mmHg)	138±13	136±12	137±12	139±13	138±13	135±11*
DBP (mmHg)	80±9	78±9	78±8	79±8	80±8	78±9*

SBP, systolic blood pressure; D BP diastolic blood pressure; HR, heart rate.
Statistical comparisons are between start and end values; *P<0.05, ***P,0.001

Author Conclusion:

High-calcium milk enriched with potassium has a small hypotensive effect in healthy people aged over 40 years.

Reviewer Comments:

The randomized controlled trial is considered the most reliable form of scientific evidence because it eliminates all forms of spurious causality. The trial involves allocating treatments to subjects at random. This methodology ensures that the different treatment groups are statistically equivalent. A double-blind study denotes an especially stringent way of conducting an experiment in an attempt to eliminate subjective bias of both the part of experimental subjects and the researchers.

The limitations and critique of the study, as stated by the authors appear to be very appropriate.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes

2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A

3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes

6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	N/A
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes

	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes